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Cocaine and ANCA associated vasculitis-like syndromes – A case series

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# Cocaine and ANCA associated vasculitis-like syndromes – a case series

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**Keywords**

Anti-Neutrophil Cytoplasmic Antibody, ANCA associated vasculitis, Drug-induced Vasculitis, Cocaine Induced midline lesion, Nasal disease, Vasculitis mimics

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**Ethics and Consent**

Analysis of the patient's electronic medical records and clinic correspondence was undertaken as part of a service evaluation of routine clinic practice using anonymised data. Application of the NHS Health Regulatory Agency research decision aid toolkit confirmed that formal Research Ethics Committee approval was not required.

**Conflicts of Interest**

The authors have no conflicts of interest to declare.

**Abbreviations**

Anti-neutrophil cytoplasmic antibody (ANCA)

Computerised tomography (CT)

Ear, nose and throat (ENT)

Cytoplasmic anti-neutrophil cytoplasmic antibody (C-ANCA)

Perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA)

Myeloperoxidase (MPO)

Proteinase 3 (PR3)

Granulomatosis with polyangiitis (GPA)

Cocaine-induced midline lesions (CIMDL)

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Human Neutrophil Elastase (HNE)

**Abstract**

**Objectives**

We analysed the spectrum of clinical manifestations of cocaine associated pseudovasculitis.

**Methods**

Clinical, serological, radiological and histological features of 14 patients with cocaine pseudovasculitis syndromes were included.

**Results**

Twelve patients had significant sinus thickening or erosive disease. Other multi-system manifestations included vasculitic rashes, pulmonary lesions and peripheral neuropathy. All patients had positive ANCA titres at presentation. All patients were managed with corticosteroids +/- methotrexate and co-trimoxazole, 2 patients received cyclophosphamide.

**Conclusions**

Advanced erosive nasal septal defects and atypical ANCA patterns are suggestive of cocaine induced pseudovasculitis. Complete drug cessation may negate the need for exposure to potent immunosuppressive agents.

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## Introduction

Cocaine is a potent illicit stimulant and 'class A' drug. It is the second most commonly used illicit drug amongst 16-59 year olds in England and Wales [1]. Acute intoxication with cocaine can cause euphoria and increased sociability. Cocaine is associated with multiple deleterious effects including acute psychosis, seizures, cerebrovascular accidents, cardiac arrhythmias, myocardial infarction and cardiac arrest. Cocaine has been implicated as a trigger for the development of multi-organ anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis [2-6]. It is increasingly recognised that cocaine may trigger a 'pseudovasculitis' presentation mimicking true idiopathic ANCA associated vasculitis (AAV) [6].

We describe the clinical and serological manifestations of 14 patients from a single centre presenting with syndromes closely mimicking AAV in subjects with a history of chronic cocaine use.

## Materials and Methods

We retrospectively analysed 14 patients presenting consecutively between 2000 and 2017 to the Rheumatology department at Guy's and St. Thomas' Hospitals, London. All patients disclosed chronic habitual cocaine use, although not necessarily at initial presentation. All patients had blood samples analysed for ANCA antibodies, inflammatory markers, full blood count, liver and renal profiles. Eleven patients had computerised tomography (CT) imaging of the sinuses, 8 had chest CT scans. Ten patients had tissue biopsies (renal, skin or nasal/sinus) during clinical work-up.

Analysis of the patient's electronic medical records and clinic correspondence was undertaken as part of a service evaluation of routine practice. Application of the

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NHS HRA research decision aid toolkit confirmed Research Ethics Committee approval was not required.

**Results**

There were 10 male and 4 female patients, median age 39 years (range 25-52 years). All patients disclosed cocaine exposure, albeit not necessarily at initial presentation. Nine patients admitted regular cocaine use for up to 12 years prior to their first presentation to our service, 4 patients were actively abusing cocaine at first presentation confirmed by positive urine toxicology tests (patients 10, 11, 13 and 14). The mean duration of cocaine use was 9.6 years (range 6-15 years).

Twelve patients had ear, nose and throat (ENT) involvement with sinus erosion or significant mucosal thickening on clinical and/or radiological assessment. Other clinical manifestations included vasculitic purpuric rash, inflammatory arthritis and peripheral neuropathy. Ten patients had tissue biopsies (renal, skin or sinus) during diagnostic assessment. Acute and chronic inflammatory changes were noted in all biopsy samples but no granulomas were visualised in the 10 patients who underwent sinus or nasal biopsy. One patient (patient 11) had 80% IgG4 plasma cells on nasal biopsy and raised serum IgG4 levels suggestive IgG4 disease. One patient (patient 9) had a skin biopsy with features of leucocytoclastic vasculitis. The same patient had evidence of glomerular red cell casts on urine cytology; subsequent renal biopsy suggested features of Henoch-Schonlein purpura/IgA vasculitis. No patients in our series had necrotizing glomerulonephritis, thrombotic microangiopathy or any evidence of cocaine associated cardiovascular disease.

The ANCA patterns were variable, both cytoplasmic and perinuclear ANCA patterns (C-ANCA and P-ANCA) were detected. All patients (14/14) were ANCA positive by immunofluorescence. Three patients had concordant ANCA patterns with

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proteinase 3 (PR3) / myeloperoxidase (MPO) sub-serologies. Four patients (patients 10, 11, 13, 14) had discordant ANCA patterns (P-ANCA, PR3 positive) with persistently positive ANCA on repeat assessment (all continued to abuse cocaine, confirmed on urine toxicology). Seven patients were ANCA positive but had PR3/MPO negative at first presentation. ANCA titres persisted in 8 patients despite clinical remission and patient reported drug cessation. ANCA titres were negative on repeat testing in 6 patients at serial follow-up visits after drug withdrawal and appropriate treatment.

The baseline demographics, laboratory assessments, serological status and clinical manifestations (including histological findings where available) are presented in Table 1.

All patients were managed with corticosteroids (median starting prednisolone dose 20mg daily); 10 received combination therapy with prednisolone, methotrexate and co-trimoxazole. Two patients (patients 2 and 6) each received a course of intravenous cyclophosphamide (6 x 500mg cyclophosphamide pulses fortnightly) during their clinical course. Patient 6 had cyclophosphamide adminsitered at another institution prior to his care being transferred to our unit. Patient 2 received cyclophosphamide because of advanced erosive nasal disease prior to disclosing chronic habitual cocaine usage. Nine patients (subjects 4, 6, 9, 10, 11, 12, 13, 14) remain under review in clinical remission, maintained on low dose prednisolone (median dose 7.5mg daily) +/- methotrexate in combination with co-trimoxazole with no further documented relapses. Six patients (subjects 1, 2, 3, 5, 7, 8) were lost to long-term follow-up after successful treatment for their acute illness due to recurrent non-attendance in clinic despite repeated invitation. They had however all achieved clinical remission prior to this.

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## Discussion

Cocaine induced vasculitis may be difficult to distinguish from idiopathic AAV [7, 8]. Careful assessment of clinical, histological and serological patterns is required to make an accurate diagnosis particularly when considering treatment regimens [8].

Cocaine induced disease is usually associated with localised rather than multi-system involvement and systemic upset [9, 10]. Necrosis and inflammation leading to midline sino-nasal destruction is associated with chronic cocaine use. This may be clinically indistinguishable from lesions resulting from AAV, but may be more destructive than lesions caused by granulomatosis with polyangiitis (GPA) [9]. This has been attributed to direct trauma with possible super-added infection with cocaine crystal insufflation, chemical adulterants or tissue ischaemia due to cocaine's vasoconstricting properties [11]. Destruction of the nasal columella and upper lip is not a feature of AAV but is highly suggestive of cocaine induced disease [12]. Eight out of 14 patients in our series had evidence of localized ENT or upper respiratory tract pathology with nasal septal perforations. One patient had evidence of perforation of the hard palate which is considered pathognomic of cocaine-induced midline lesions (CIMDL) [9]. **.** Renal involvement is rare with cocaine induced disease but common in AAV [13, 14]. Comprehensive renal assessment is strongly advised if symptoms are suggestive of AAV.

Histological patterns can help differentiate cocaine-induced lesions from AAV. Features including leucocytoclastic vasculitis and perivenulitis may be present in both conditions. In our series, 10 patients had tissue (renal, skin or sinus) biopsies, but no patients had granulomas evident. Extravascular inflammatory changes (including giant cells, micro-abscesses, foci of microscopic necrosis and granulomas) which are hallmarks of GPA are absent in cocaine induced disease [9].

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Although tissue biopsy is advised to support clinical diagnosis, caution must be exercised if there is sole reliance upon nasal or sinus biopsy to diagnose AAV as it may be non-diagnostic. Nasal and sinus biopsies can help in identifying atypical infections which can be destructive.

Although ANCA positivity is reported in over 50% of patients with cocaine use, the pattern is usually atypical with very high titres compared to idiopathic AAV [10]. Patients with cocaine use may test positive for both MPO and PR3 [4, 5]. Determining whether cocaine exposure induces ANCA or whether patients develop unrelated idiopathic small/medium vessel vasculitis is challenging [7]. In drug associated ANCA positive vasculitides, the presence of ANCA may not have prognostic value [15]. The detection of Human Neutrophil Elastase (HNE) antibodies offers an additional diagnostic tool in differentiating cocaine induced disease from AAV. HNE antibodies have not been described in patients with GPA or microscopic polyangiitis [16]. Unfortunately, our centre did not have access to the HNE assay which is not widely available. Of note, patient 11 had features suggestive of IgG4 related disease on nasal biopsy. The clinical manifestations of IgG4 disease and ANCA associated vasculitis may overlap and low titre ANCA in IgG4 disease may not be an unexpected finding [17].

Levamisole (a synthetic imidazothiazole derivative previously used as an immunomodulatory and anti-helminthic agent in human and veterinary medicine) is a common adulterant of cocaine [18]. Levamisole may potentiate and enhance the psychoactive drug effects but has led a distinct clinical phenotype with neutropenia, agranulocytosis and retiform purpura that closely mimics AAV [19, 20]. Levamisole, can cause loss of tolerance to multiple neutrophil-specific proteins leading to high titre ANCA positivity; MPO and PR3 are frequently detected in addition to anti-

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nuclear antibodies, lupus anticoagulant and hypocomplementaemia. Autoantibodies are also formed to HNE, cathepsin G, and lactoferrin [10, 21]. Detecting levamisole is a challenging due to its short half-life and small percentage excretion detectable in the urine. Recognising the characteristic clinical manifestations may enable accurate diagnosis and inform therapy [22].

Urine toxicology can be used to confirm cocaine exposure. Drug metabolites (most commonly benzoylecgonine) are detectable within 2 hours of use up to 5 days. Only 4 patients in our series had positive urine toxicology, the remaining subjects had either reported completed cessation of cocaine use or were outside the time frame for testing. Urine toxicology screening is preferable to saliva and blood toxicology testing due to cost effectiveness and ready availability. We acknowledge that patient reported drug cessation may be unreliable given the reluctance to admit using illegal substances. It is therefore challenging to accurately determine the period between patient reported drug use and onset of vasculitis symptoms.

Idiopathic AAV requires treatment with potent immunosuppressive agents with potential toxicity and associated mortality. In cocaine associated vasculitis, drug cessation may result in clinical resolution, negating the requirement for escalation of immunosuppression above corticosteroids [6]. Most patients in our series were successfully managed with either corticosteroid alone or in combination with steroid sparing agents. Standard management guidelines for AAV may not be directly applicable to this group of patients. Treatment paradigms should reflect disease severity and degree of organ involvement.

Chronic cocaine use may be associated manifestations that closely parallel ANCA associated vasculitis. A comprehensive drug history is a necessity due to

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possible reluctance to admitting recreational drug use. Urine drug screens should be openly discussed with patients. This group of patients may be challenging to treat due to variable adherence to therapy and long term follow-up. Referral to drug rehabilitation services to assist with managing the physical and psychosocial aspects of drug addiction is advised.

**Key Messages**

- Differentiating cocaine induced pseudovasculitis from idiopathic AAV is clinically challenging; a thorough drug history and high index of suspicion are key
- Advanced erosive nasal septal defects and atypical ANCA patterns are suggestive of cocaine induced pseudovasculitis
- Complete drug cessation may help negate the need for potent immunosuppressive therapy

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| | | | | | | | | System specific clinical manifestations | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient** | **Sex** M/F | **Age** (years) | **ESR** (mm/h) | **CRP** (mg/L) | **Serology** (U/ml) | **Creatinine** (μmol/L) | **Duration of cocaine use prior to first presentation (years)** | **Inflammatory arthritis** | **Skin (vasculitic purpuric rash)** | **Peripheral neuropathy** | **Pulmonary lesions** | **ENT lesions** | **Tissue histology** |
| **1** | F | 25 | 18 | 10 | C-ANCA + PR3 57.5<br>Repeat ANCA - | 64 | 6 | + | + | - | None (X-ray) | Mucosal thickening maxillary antra. Nasal septum deviation with large defect within it. | **Sinus biopsy**: granulation tissue, no evidence of vasculitis. |
| **2** | F | 39 | 37 | 127 | P-ANCA + MPO 22<br>Repeat ANCA - | 74 | 12 | + | - | - | None (CT) | Mucosal thickening maxillary antrum and ethmoid sinuses, nasal septum deviation and destruction of posterior aspect. Destruction of the nasal columella and upper lip. | **Sinus biopsy**: fibrosis, acute and chronic inflammation. Necrosis at the surface with deeper, microscopic foci of stromal necrosis. Foci of acute venular inflammation, no fibrinoid necrosis. Polymorphic inflammatory cell infiltrate. No granuloma seen. |
| **3** | M | 37 | 25 | 47 | C-ANCA + PR3/MPO –<br>Repeat ANCA - | 92 | Unconfirmed | - | - | + | None (X-ray) | Mucosal thickening, abnormal soft tissue surrounding middle and lower turbinates with erosion and nasal septal deviation. | **Sinus biopsy**: ulcerated granulation tissue with dense inflammatory infiltrate with neutrophils, lymphocytes.<br>**Renal biopsy**: moderate haematuria. Marked fibro-intimal thickening of medium caliber arteries, no evidence of acute thrombotic microangiopathy. Several foci of hyaline arteriosclerosis. Small focus of interstitial fibrosis. No glomerulonephritis. |
| **4** | F | 39 | 30 | 33 | P-ANCA + PR3/MPO –<br>Repeat P-ANCA + | 60 | 10 | + | - | + | Solitary nodule and calcified granuloma (CT) | Maxillary antrum mucosal thickening. Thickening of osteomeatal | - |

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| | | | | | PR3/MPO - | | | | | | | complex. | |
| **5** | M | 43 | 11 | 10 | P-ANCA + PR3/MPO – Repeat ANCA - | 99 | Unconfirmed | + | - | + | Calcification (CT) | Mucosal thickening of ethmoid sinuses. Polyploid thickening of right maxillary sinus. Thickened mucosa of middle and inferior turbinates. | **Sinus biopsy**: active chronic inflammation with a focus of necrotizing vasculitis, fibrinous necrosis and acute inflammation of a venule. No granuloma. |
| **6** | M | 38 | 20 | 5 | C-ANCA + PR3 381 Repeat C-ANCA + PR3 8.3 | 59 | 15 | - | + | - | Left hilar nodes and lower lobe mass (CT) | Air fluid level with associated mucosal thickening. Nasal septal deviation. | **Sinus biopsy**: ulceration with fibrin deposition and acute on chronic inflammation with plasma cells, neutrophils and lymphocytes. No granuloma or vasculitis seen. |
| **7** | M | 39 | 10 | 1 | P-ANCA + PR3/MPO – Repeat C-ANCA + PR3/MPO - | 99 | Unconfirmed | + | - | - | Multi-lobar consolidation, opacification, nodularity (CT) | Air fluid level in right maxillary antrum. Mucosal thickening of ethmoid air cells. Nasal septal deviation. | - |
| **8** | M | 41 | 5 | 25 | C-ANCA + PR3/MPO – Repeat ANCA - | 90 | 10 | + | - | + | None (X-ray) | Mucosal thickening within maxillary antra. Mild deviation cartilaginous nasal septum with extensive septum defect. Minimal mucosal thickening within sphenoid sinus and ethmoid air cells. | - |

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| **9** | M | 53 | 5 | 5 | C-ANCA + PR3/MPO –<br><br>Repeat ANCA - | 91 | 10 | + | + | - | None (X-ray) | - | **Renal biopsy**: mesangial proliferative glomerulonephritis with crescents. IgA and fibrinogen deposition in mesangial matrix. Complement Deposition. Appearances suggestive of Henoch Schonlein Purpura.<br><br>**Skin biopsy**: florid leucocytoclastic vasculitis. Mild superficial perivascular predominantly neutrophilic inflammatory cell infiltrate with leucocytoclastic, extravasated erythrocytes. |
| **10 *** | M | 45 | 18 | 10 | P-ANCA + PR3 69<br><br>Repeat P-ANCA + PR3/MPO - | 111 | 10 | + | - | - | Pleural thickening (CT) | Concentric mucosal hypertrophy of maxillary antra with perforation in lower bony septum. | **Sinus biopsy**: Marked inflammatory change, densely inflamed granulation tissue with lymphocytes, neutrophils and plasma cells. |
| **11 *** | M | 40 | 39 | 4 | P-ANCA + PR3 + 4.2<br><br>Repeat P-ANCA + PR3/MPO - | 73 | Unconfirmed | + | - | - | Unremarkable appearances (CT) | Mucosal thickening within bilateral middle and inferior meati. Erosion of floor of nasal cavity, hard palate and nasal septum. | **Nasal biopsy**: inflammatory features with ulceration, no evidence of vasculitis, granuloma or malignancy. IgG4 plasma cells >80%. Sclerosing/eosinophilic angiocentric fibrosis noted. |
| **12** | M | 38 | 40 | 33 | P-ANCA + PR3/MPO –<br><br>Repeat P-ANCA + PR3/MPO - | 76 | Unconfirmed | - | - | - | Non-specific pulmonary nodules (CT) | Irregular thickening in nasal vestibule extending in to inferior meatus. Occlusive tissue in left middle meatus. No osseous or destructive lesion. Mild to moderate polyploid mucosal thickening of the maxillary antra and anterior ethmoid | **Nasal biopsy:** widespread mixed inflammatory infiltrate of neutrophils, lymphocytes, plasma cells and macrophages. No significant eosinophil infiltrate. Vascular necrosis and inflammation nasal ulceration. |

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| | | | | | | | | | | | | air cells. | |
| **13 *** | M | 37 | 2 | 3 | P-ANCA + PR3 + 22.0, MPO –<br><br>Repeat P-ANCA + PR3 + 16, MPO - | 99 | 6 | + | - | + | None (X-Ray) | Patchy mucosal thickening within maxillary and ethmoid sinuses bilaterally, Nasal septal thickening of left middle/inferior turbinates. Perforation anteriorly and crowding of left nasal cavity | **Nasal biopsy:** fibrin slough with dense neutrophil infiltrate. Acute inflammation. |
| **14 *** | F | 32 | 32 | 15 | P-ANCA + PR3 + 18 MPO –<br><br>Repeat P-ANCA + PR3 + 15, MPO - | 53 | 7 | - | + | - | None (X-Ray) | Sinonasal mucosal thickening, obstruction of left ostiomental complex. Bony erosion of the sphenoid sinus floor with bony sclerosis. | - |

**Table 1: Demographics, serology and organ involvement of eleven patients with ANCA-associated vasculitis induced by cocaine**. ESR – Erythrocyte Sedimentation Rate, CRP – C-Reactive Protein, ENT – Ear, Nose and Throat, CT – Computerised Tomography, C-ANCA - cytoplasmic anti-neutrophil cytoplasmic antibody, P-ANCA - perinuclear anti-neutrophil cytoplasmic antibody, MPO – myeloperoxidase, PR3 - proteinase 3,* positive urine toxicology confirming recent cocaine exposure.

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